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The Honorable Nancy Landon Kassebaum
Chairman, Committee on Labor
and Human Resources
United States Senate

Dear Madam Chairman:

Under current law, U.S. pharmaceutical manufacturers must obtain approval from the Food and Drug Administration (FDA) to export drugs for marketing that are not approved for sale in the United States. Further, unapproved drugs may only be exported from the United States to 21 designated countries if these countries have approved the drugs for sale. Many in Congress are concerned that such restrictions on exports cost American jobs, create an incentive for firms to build new manufacturing facilities overseas, and deny American-manufactured drugs to countries whose own regulatory systems have approved them.

The FDA Export Reform and Enhancement Act of 1995 (S. 593) would permit manufacturers to export pharmaceutical products for sale that have not been approved for marketing in the United States without prior FDA approval.[1] In general, the bill establishes two methods for unapproved drugs to be exported for marketing in a foreign country. First, an unapproved drug could be exported to a country named in the bill (called a tier I country) or any other country provided that the drug complies with the laws of that country and has valid marketing authorization by the appropriate approval authority in a tier I country.[2] Second, an unapproved drug

[1]The bill also includes provisions for exporting unapproved animal drugs, biological products, and medical devices. This letter considers only drugs.

[2]The tier I countries listed in S. 593 are Australia, Canada, Israel, Japan, New Zealand, Switzerland, and any country in the European Union or within the European Economic Area (including, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden,

155894

could be exported to any other country not named in the bill (called a tier II country) provided the country has an "adequate regulatory system to protect the health of its citizens."

This letter responds to your request that we assist the Committee by (1) suggesting criteria that could be used by Congress to identify countries that have adequate regulatory systems to protect the health of their citizens and (2) determining the implications of applying these criteria to different countries.[3]

To identify possible criteria for assessing the adequacy of countries' drug regulatory systems, we interviewed officials from FDA, the World Health Organization (WHO),[4] the Department of Commerce, the U.S. Trade Representative, and several pharmaceutical and biotechnology companies. We also interviewed representatives from the Pharmaceutical Research and Manufacturers of America, the Health Industry Manufacturers Association, and the Biotechnology Industry Organization. We reviewed WHO's "Indicators for Monitoring National Drug Policies," "The World Drug Situation," and "Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce." Based upon our review of these documents, we identified criteria from information developed by WHO and criteria in the Drug Exports Amendments Act of 1986 (P.L. 99-660).

To determine the implications of applying these criteria to potential tier II countries, we performed three tasks. First, we identified countries with the highest gross national product values in 1993, excluding those countries included in tier I under S. 593. As agreed with your staff, we limited our assessment to the 20 largest economies. Second, we reviewed the International Federation of Pharmaceutical Manufacturers Associations' (IFPMA) Compendium on Regulation of Pharmaceuticals for Human Use for background information on the drug regulatory systems of

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Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, and United Kingdom.

[3]In this letter, criteria refers to the elements or characteristics of a country's drug regulatory system.

[4]WHO is a specialized agency of the United Nations with primary responsibility for international health matters and public health.

20 countries.[5] Third, we compared the criteria with descriptions contained in the Compendium to determine the extent to which the countries appeared to satisfy the criteria. The Compendium, however, did not contain enough information to determine whether or not countries completely satisfied the criteria. As a result, we were only able to assess whether elements of the criteria were present in the legal framework of the countries. We did not independently verify the accuracy of the information contained in the Compendium or determine the extent to which the countries have implemented or enforced the systems described in the Compendium. Our work was performed between September and November 1995 in accordance with generally accepted government auditing standards.

In summary, we found that WHO has compiled extensive information on national pharmaceutical policies and programs that can be used to assess the adequacy of a country's system for regulating pharmaceutical products. FDA officials and industry representatives agreed that criteria in the Drug Exports Amendments Act of 1986 and information developed by WHO provide a reasonable basis for identifying criteria for assessing the adequacy of a drug regulatory system. Our criteria, based on such information, are the presence of drug legislation, regulations, and regulatory bodies that govern and control major aspects of pharmaceutical activities, including registering drugs that have been assessed to be safe and efficacious and ensuring that drugs are of an acceptable quality and that a mechanism exists to report and monitor adverse drug reactions.

When these criteria are applied to non-tier I countries with the 20 largest economies, information contained in the IFPMA Compendium suggests that most have the legal and organizational framework necessary to maintain an adequate drug regulatory system. For example, the majority of countries have written laws and regulations governing the control of imported drugs. However, the criterion on the presence of an adverse drug reaction (ADR) system that we believe is important to protect citizens from potentially serious adverse reactions is mandated in 16 of the 20 countries. ADR reporting is voluntary in the others.

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[5]We also excluded several countries (Ukraine, Romania, Belarus, and Kazakhstan) because they were not contained in the IFPMA Compendium.

BACKGROUND

The Drug Exports Amendments Act of 1986 authorizes the export, for commercial marketing abroad, of veterinary and human drugs not approved for marketing in the United States to 21 specific countries under certain conditions.[6] An application must be submitted to FDA that contains certification by the applicant that the drug is approved for marketing in each country to which it is to be exported, that it is manufactured in conformity with good manufacturing practices, and that it is properly labeled. The applicant must also be actively pursuing approval or licensing of the drug in the United States.

Under the act, changes in the list of 21 countries to which drugs may be exported must be based on a country satisfying certain criteria. Specifically, a country must have statutory or regulatory (1) authority to approve drugs after reviews by qualified government experts have determined them to be safe and effective on the basis of adequate and well-controlled investigations, including clinical investigations; (2) requirements that drugs are manufactured in accordance with good manufacturing practices that preserve the identity, quality, purity, and strength of the drugs; (3) requirements for the reporting of adverse reactions to drugs and removal of drugs found not to be safe or effective; and (4) requirements that the labeling and promotion of drugs be in accordance with the approval of the drugs.

Manufacturers exporting drugs are often asked by foreign governments to supply a certification from FDA attesting that the drugs being exported (1) are freely marketed in the United States; (2) comply with U.S. laws and regulations; (3) comply with the importing country's requirements;[7] (4) meet certain national or international standards, such as quality standards; and (5) do not contain contaminants. FDA's certification process may include the issuance of a

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[6]Under the act, unapproved drugs can be exported to Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

[7]FDA expects the manufacturer to submit a copy of the foreign country's approved labeling, including an English translation.

certificate to accompany the exported drug, such as, a Certificate of Free Sale.

Internationally, the "WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce" provides information to importing countries on the quality of pharmaceutical products.[8] The scheme offers information about whether or not a drug is approved for marketing in the country of export and if the manufacturer of the drug is routinely inspected for compliance with good manufacturing practices (GMPs).[9]

CRITERIA FOR IDENTIFYING COUNTRIES WITH ADEQUATE REGULATORY SYSTEMS

While information for assessing highly evolved national drug regulatory systems is readily available, information for assessing the adequacy of lesser developed regulatory systems is all but nonexistent. In discussions with FDA officials and industry representatives, they suggested that we look to the criteria in the act and WHO for such information. Through its efforts to assist countries in formulating and implementing comprehensive national drug policies, WHO has analyzed the world drug situation and developed indicators to assess countries' progress in implementing national drug policies.

Based on the act and WHO indicators for monitoring national drug policies, we developed criteria for evaluating whether potential tier II countries have adequate regulatory systems.[10] The criteria fall into two categories. The first category focuses on the laws and legal framework a country should have to control drug regulation and distribution. The second category of criteria requires that a country undertake certain regulatory activities. These activities include controls over the safety and quality of pharmaceutical products.

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[8]The WHO Certification Scheme applies to drug substances and finished dosage forms intended for human use as well as veterinary products administered to food-producing animals.

[9]As of December 1994, the scheme has been accepted by health authorities in 138 countries.

[10]We adapted criteria from the "Indicators for Monitoring National Drug Policies," WHO (Geneva: 1994).

Legal Framework

Legislation: An importing country must have drug legislation that describes the legal conditions under which pharmaceutical activities should be organized, including drug importation, distribution, production, registration, and licensing. Drug legislation is intended to ensure drug safety, efficacy, and quality and to regulate production and dispensing.

Regulations: An importing country must have regulations that govern the standards and procedures for carrying out drug legislation. Regulations provide the legal machinery to achieve the administrative and technical goals. Most pharmaceutical activities must be covered by regulations. These describe, for example, the obligations of importers, their responsibilities, and the sanctions if they do not fulfill them.

Regulatory Authority: An importing country must have a regulatory body that controls the registration, licensure, and quality of drugs and ensures that drug legislation and regulation are enforced.

Regulatory Activities

Registration: The importing country must have a registration procedure for granting marketing authorization (approval) after an application to market a product has been evaluated, that uses established criteria to determine the product's safety, efficacy, and quality.

Quality Assurance: An importing country must have a system of quality assurance that ensures that drugs being produced, entering, or circulating in that country are of acceptable quality. This includes analyzing and regularly checking all drugs used within a country. A quality assurance system may be used in combination with a well-organized registration system and systematic certification of GMPs or certification schemes in ensuring drug quality.

Monitoring of Adverse Drug Reactions: The importing country must have a system that requires the collection and assessment of data on suspected adverse drug reactions. If unknown contraindications or serious adverse reactions are observed, it is particularly important that such incidents be reported to a central authority so that a reassessment of the drug's safety can be made and that unsafe drugs can be taken off the market.

IMPLICATIONS OF APPLYING
CRITERIA TO DIFFERENT COUNTRIES

While assessing the extent to which countries satisfied the criteria was difficult, we were able to link the criteria to specific elements of each country's drug regulatory system by using information from the IFPMA Compendium.

Table 1 shows the presence of drug legislation, regulations, regulatory authorities, registration, quality assurance, and ADR systems in selected countries. According to the IFPMA Compendium, drug legislation and regulations refer to the major laws and regulations upon which the product authorization system is based and supplementary legislation related to the law. The regulatory body is responsible for assessing and authorizing the marketing of pharmaceutical products. Generally, such authorizations are concerned with safety, efficacy, and quality. Registration is a system for the control and sale of medicinal products. Registration usually consists of a permit issued from a government agency for a medicinal product to be made available on a commercial basis. Quality assurance indicates that the country requires that medicinal products be manufactured in accordance with a code of quality assurance procedures (GMPs) to safeguard the quality of the end product by a company that holds a manufacturer's authorization. Also, most regulatory authorities have laboratories available for testing the quality of products either as part of the evaluation procedure for new products or as part of the control of imported and marketed products. ADR indicates that the country has a national system for requiring manufacturers to report adverse drug reactions.

Table 1: Selected Countries with the Necessary Structural Elements for Implementing a Drug Regulatory System

Country	Legislation	Regulations	Regulatory body	Registration	Quality assurance	ADR
China	X	X	X	X	X	X
Russia	X	X	X	X	X	X
Brazil	X	X	X	X	X	
Mexico	X	X	X	X	X[a]	
South Korea	X	X	X	X	X	X
India	X	X	X	X	X	X
Argentina	X	X	X	X	X	
Taiwan	X	X	X	X	X	X
Poland	X	X	X[b]	X[c]	[d]	X
Indonesia	X	X	X	X	X	X
Saudi Arabia		X	X	X		
Turkey	X	X	X	X	X	X
Thailand	X	X	X	X	X[e]	X
South Africa	X	X	X	X	X	X
Czech Republic	X	[f]	X	X	X	X
Hungary	X	X	X	X	X	X
Malaysia	X	X	X	X	X	X
Venezuela	X	X	X	X	X	X
Singapore	X	X	X	X	X	X
Philippines	X	X	X	X	X	X

Note: X indicates whether the country appears to meet these criteria. Our determination about whether a country satisfies the criteria is based solely on information in the 1994 IFPMA Compendium. It is possible that there may be other indicators not described in the Compendium that may satisfy our criteria. For example, a country's participation in the "WHO

Adverse Reaction Monitoring Scheme" may be used to satisfy the ADR criteria.

Countries are listed in descending order by gross national product in 1993 dollars as tabulated by the U.S. Arms Control and Disarmament Agency, "World Military Expenditures and Arms Transfers 1993-1994" (1995).

[a]Good laboratory practices are imposed, and the authorities inspect laboratories to assure compliance. New regulations, however, are in preparation on standards, such as, stability and GMPs, which previously were handled as guides.

[b]The organizational development of Poland's new regulatory authority is still underway.

[c]All pharmaceutical agents and medical products are subject to registration except other agents and products selected by the Minister of Health and Social Welfare.

[d]GMP requirements will come into force in 1997. GMP certificates are required for imported drugs to prove that the manufacturer is subject to regular inspections.

[e]The WHO's GMP standards are observed in principle.

[f]We cannot determine the presence of regulations from information in the Compendium.

The table also shows that most countries have written laws and regulations covering various aspects of drug regulatory control, registration, and quality assurance. Furthermore, all the countries have a regulatory body that is responsible for issuing marketing authorizations for pharmaceutical products. Quality assurance in the form of countries enforcing GMPs is present in 18 of the 20 countries. According to the Compendium, however, Poland and Saudi Arabia do not enforce GMPs. For the purposes of this analysis, we accepted the presence of GMPs as an indication of quality assurance. In addition, 16 of the 20 countries assessed have national systems that require manufacturers to report adverse drug reactions to a central government authority. Of the 4 countries that do not have mandatory reporting requirements, manufacturers or physicians report adverse drug reactions to authorities on a voluntary basis. Whether or not a voluntary system could adequately monitor adverse drug reactions cannot be determined from information in the Compendium.

A comprehensive system of quality assurance of pharmaceutical products must be based on a reliable system of evaluation and registration to establish safety and efficacy, analysis of the quality of the finished drug product, and confirmation that products are manufactured in accordance with GMPs. Because most countries lack such a comprehensive system to assess the quality of drugs they

import, they rely on a certification scheme to establish the safety and efficacy of imported drugs. Under the certification scheme, the regulatory authority of the exporting country prepares a certificate attesting that a drug is registered and authorized for sale (freely marketed) in that country. We found that almost all the countries reviewed require importers to provide such certificates. Because drugs not approved in the United States cannot be certified as being freely marketed, importing countries will have to assess the safety and adequacy of these drugs or rely on the approval of such drugs in tier I countries.

In addition, WHO plans to complete two studies by the end of 1995 that will provide additional help in determining criteria that could be used to assess the adequacy of countries' drug regulatory systems. One study is an update of "The World Drug Situation," which will include WHO's assessment of the extent to which 193 countries have adopted regulatory criteria suggested by WHO. The second study will identify criteria that WHO considers essential for any country to develop to help protect against the importation of unsafe human drugs.

We obtained technical comments from FDA officials and pharmaceutical representatives on a draft of this letter that have been incorporated where appropriate. A draft of this letter also was reviewed by WHO officials. While WHO officials acknowledged that their standards may be useful for assessing a country's drug regulatory system, they would not provide further comments with regard to the adequacy and effectiveness of our criteria.

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The information in this letter was prepared by John C. Hansen, Assistant Director; Gloria Taylor; Elise Bornstein; and Joel Hamilton under the direction of Mark V. Nadel. Please call Mr. Hansen at (202) 512-7105 if you or your staff have any questions.

Sincerely yours,

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